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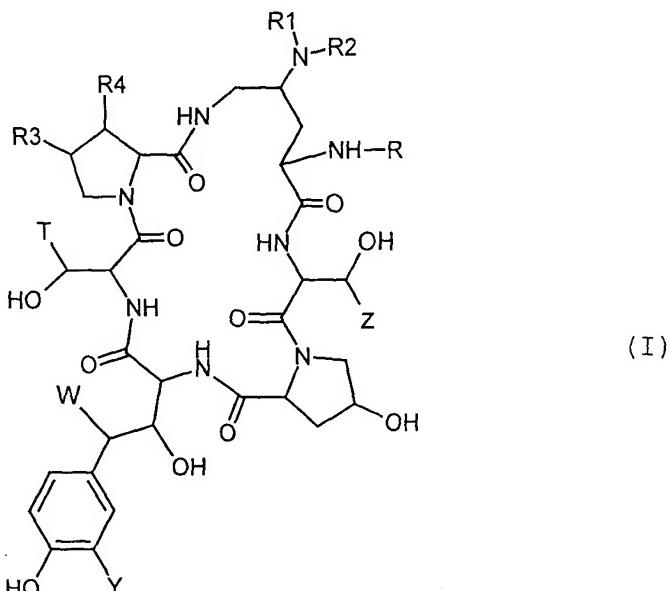
New derivatives of echinocandine, their preparation process  
and their use as antifungals.

-- This is a 371 of PCT/FR00/01568 filed June 8, 2000.--

The present invention relates to new derivatives of  
5 echinocandine, their preparation process and their use as  
antifungals.

A subject of the invention is, in all possible isomer  
forms as well as their mixtures, the compounds of formula  
(I):

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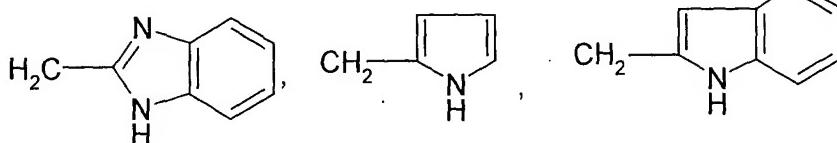
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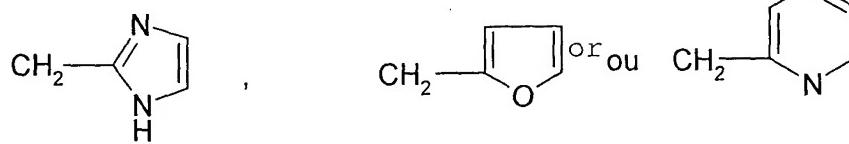
in which

25 either R<sub>1</sub> represents a hydrogen atom or a methyl radical.  
R<sub>2</sub> represents a cyclohexyl radical substituted by an amine, a  
CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>3</sub> radical, a CH<sub>2</sub>CHCH<sub>3</sub>NH<sub>2</sub> radical, a

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radical, a CHCH<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub> radical, a -(CH<sub>2</sub>)<sub>a</sub>OH radical, a

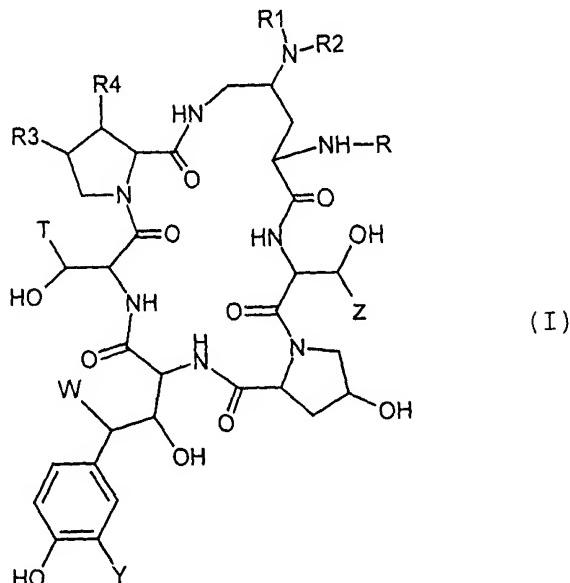
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146:1375  
MARKED-UP VERSION  
OF  
CLAIMS*A compound selected from the group consisting of*1) */ all possible isomeric forms as well as their mixtures,  
the compounds of formula (I).*

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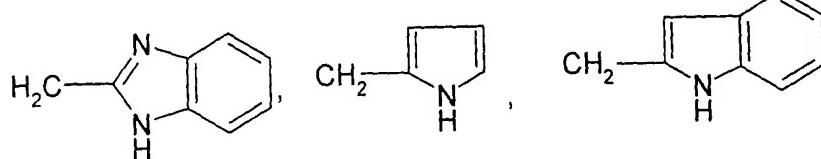
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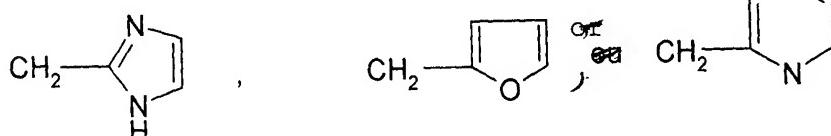
in which  
 either  $R_1$  represents a hydrogen atom or a methyl radical,  
 $R_2$  represents a cyclohexyl radical substituted by an amine, a  
 CH<sub>2</sub>CH<sub>2</sub>NHCH<sub>3</sub> radical, a CH<sub>2</sub>CHCH<sub>3</sub>NH<sub>2</sub> radical, a

*is selected from the group consisting of*

25



30



radical, a CHCH<sub>3</sub>CH<sub>2</sub>NH<sub>2</sub> radical, a -(CH<sub>2</sub>)<sub>a</sub>OH radical, a  
 representing an integer comprised between 1 and 8, a (CH<sub>2</sub>)<sup>b</sup>-  
 C≡N radical where  
 b representing an integer comprised between 1 to 8, a  
 CHCH<sub>3</sub>C<sub>6</sub>H<sub>5</sub> radical, a (CH<sub>2</sub>)<sub>a</sub>-C(CH<sub>3</sub>)<sub>2</sub>NHCOCF<sub>3</sub> radical, a and

$\text{CHCH}_3(\text{CH}_2)_d$  radical,  $d$  representing an integer comprised between 1 <sup>to</sup> 8

or  $R_1$  and  $R_2$  together with the nitrogen <sup>to which they are attached</sup> which carries them form a ring <sup>with</sup> 3, 4 or 5 carbons optionally substituted by

5 an amine

$R_3$  represents a hydrogen atom, a methyl <sup>and</sup> hydroxyl radical

$R_4$  represents a hydrogen atom or a hydroxyl radical

$R'$  represents a linear or branched <sup>alkyl and</sup> cyclic <sup>alkyl of</sup> chain containing up to 30 carbon atoms, optionally containing one or more

10 heteroatoms, <sup>at least</sup> one or more heterocycles <sup>and a linear, branched</sup> or cyclic acyl radical containing up to 30 carbon atoms <sup>at least</sup> optionally containing one or more heteroatoms <sup>at least</sup> and/or one or more heterocycles,

T represents a hydrogen atom, a methyl radical,  $\text{--CH}_2\text{CONH}_2$ ,  
 15  $-\text{CH}_2\text{C}\equiv\text{N}$  radical,  $\text{--}(\text{CH}_2)_2\text{NH}_2$  or  $-(\text{CH}_2)_2\text{Nalk}^+\text{X}^-$  radical, X being a halogen atom and alkyl <sup>is</sup> alkyl radical containing up to 8 carbon atoms,

Y represents a hydrogen atom, a hydroxyl radical or a halogen atom <sup>and</sup> or an  $\text{OSO}_3\text{H}$  radical or one of the salts <sup>thereof</sup> of this radical,

20 W represents a hydrogen atom or an OH radical,

Z represents a hydrogen atom or a methyl radical <sup>and it is non-toxic</sup>, <sup>is</sup> as well as the addition salts with acids of the products of formula (I).

2) The compounds of formula (I) defined in claim 1 in which

25 T represents a hydrogen atom.

3) The compounds of formula (I) defined in claim 1 <sup>or</sup> 2 in which W represents a hydrogen atom.

4) A The compounds of formula (I) defined in any one of claims 1 to 3, in which Z represents a methyl radical.

30 5) A The compounds of formula (I) defined in any one of claims 1 to 4 in which Y represents a hydrogen atom.

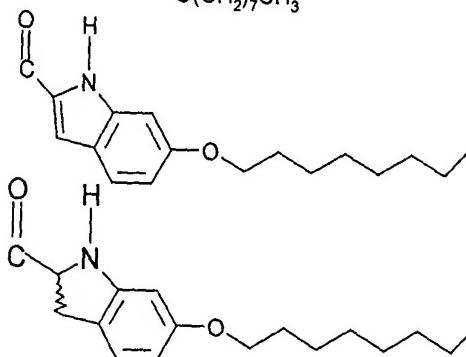
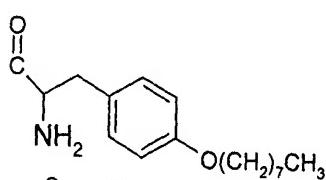
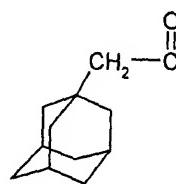
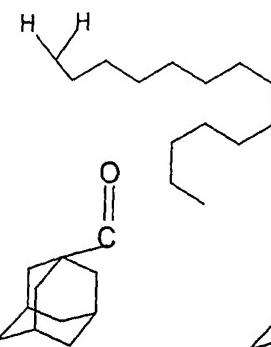
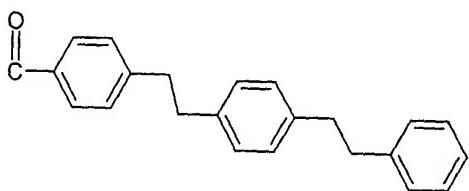
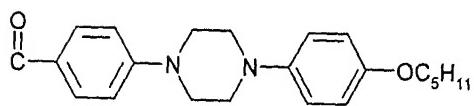
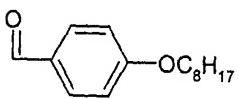
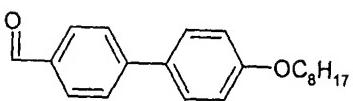
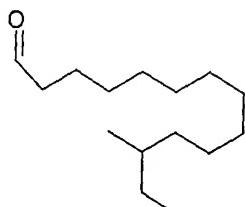
6) A The compounds of formula (I) defined in any one of claims 1 to 5 in which  $R_3$  represents a methyl radical.

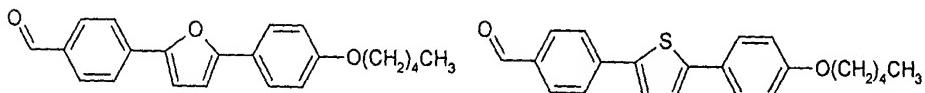
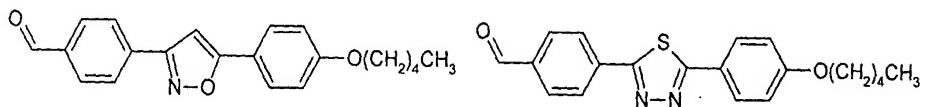
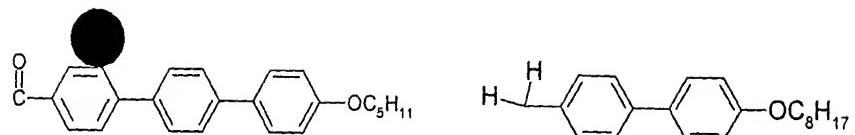
7) A The compounds of formula defined in any one of claims 1

35 to 6 in which  $R_4$  represents a hydroxyl radical.

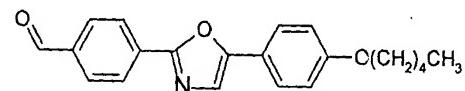
8) The compounds of formula (I) defined in any one of claims 1 to 7 in which R is selected from the group consisting of

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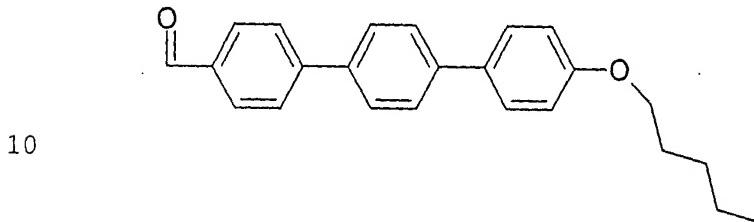


and



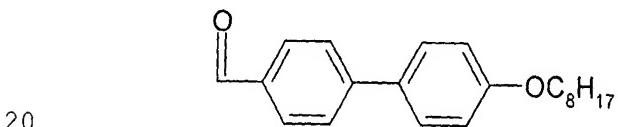
radical.

- 9) ~~The compounds of formula (I) defined in claim 8, in~~  
 5 which R ~~represents a~~ <sup>is</sup>



chain.

- 15 10) ~~The compounds of formula (I) defined in claim 8, in~~  
 20 which R ~~represents a~~ <sup>is</sup>

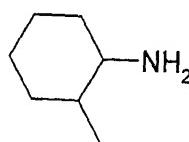


chain.

- 11) ~~The compounds of formula (I) defined in any one of~~  
 claims 1 to 10 in which R<sub>1</sub> is a <sup>hydrogen</sup> ~~hydrogen atom~~.

- 12) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 11 in which R<sub>2</sub> is ~~a~~

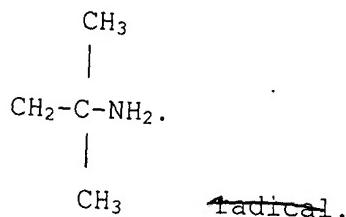
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~~radical.~~

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- 13) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 11 in which R<sub>2</sub> is ~~selected from the group consisting of~~
- $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}_2\text{-CH-NH}_2 \text{ radical, } \end{array}$  ~~a~~  $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH-CH}_2\text{NH}_2 \text{ radical or a} \end{array}$  ~~and~~

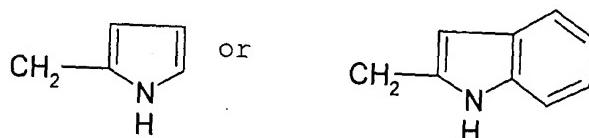
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- 14) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 11 in which R<sub>2</sub> is ~~a~~

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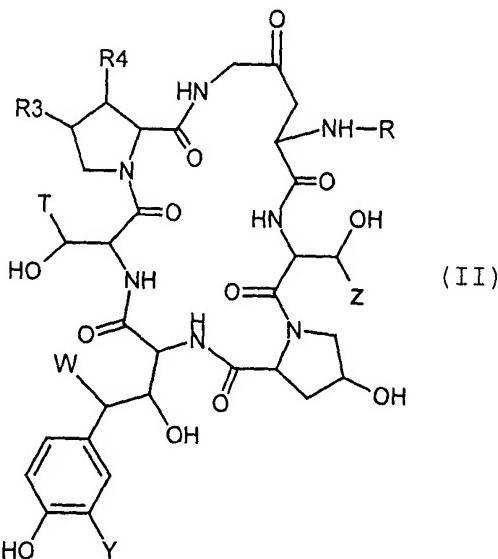
~~radical.~~

- 15) ~~The~~ compounds of formula (I) defined in any one of claims 1 to 14 ~~the names of which follow:~~

- 1-[4-[(1H-benzimidazol-2-yl)-methyl]-amino]-N2-[[4"- (pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer B), ~~and~~
- trans 1-[4-[(2-aminocyclohexyl)-amino]-N2-[[4"- (pentyloxy)[1,1':4',1"-terphenyl]-4-yl]-carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]5-L-serine-echinocandine B trifluoroacetate (isomer A).

16) A process for the preparation of compounds of formula (I) defined in any one of claims 1 to 15 characterized in that a compound of formula (II)

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wherein  
is which R, R<sub>3</sub>, R<sub>4</sub>, T, Y, W and Z retain their previous meaning, is subjected to the action of an amine or amine derivative capable of introducing

the  $\begin{array}{c} \text{R}_1 \\ | \\ \text{N} \\ | \\ \text{R}_2 \end{array}$  radical in which R<sub>1</sub> and R<sub>2</sub>

are defined as in claim 1  
retain their previous meaning and if desired to the action of  
a reducing agent  
and/or an amine functionalization agent,  
and/or an acid in order to form the salt of the product of claim 1,  
obtained,

and/or a separation agent of the different isomers obtained,  
and the sought compound of formula (I) is thus obtained.

17) As antifungal compounds, the compounds of formula (I) defined in any one of claims 1 to 15, as well as their addition salts with acids.

18) The pharmaceutical compositions containing at least one compound of formula (I) defined in any one of claims 1 to 15 as a medicament, as well as their addition salts with pharmaceutically acceptable acids.

--19. An antifungal composition comprising an antifungally effective amount of a compound of claim 1 and an inert pharmaceutical carrier.

20. A method of treating fungal infections in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antifungally effective amount of a compound of claim 1.--

REMARKS

The amendment is submitted to insert reference to the PCT application, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,  
BIERMAN, MUSERLIAN AND LUCAS

  
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CAM:sd

Enclosures: Marked-Up Version of Specification and Claims  
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